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Attorney's Docket No. 12.006011

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Love et al.		
Appl. No.:	09/410,336	Group Art Unit:	1642
Filed:	October 1, 1999	Examiner:	Stephen Rawlings
For:	MEHODS FOR IDENTIFICATION, DIAGNOSIS, AND TREATMENT OF BREAST CANCER		

August 12, 2005

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

APPELLANTS' REPLY BRIEF

Sir:

This Reply Brief is filed in response to the "Examiner's Answer" mailed June 24, 2005.

INTRODUCTION

In the Examiner's Answer mailed June 24, 2005, the Examiner presented arguments relating to issues 1 and 2 of Appellants' Appeal Brief mailed April 15, 2005. Accordingly, Appellants here responds to the arguments presented in the Examiner's Answer.

ARGUMENT

I. The prior art references of Yoshimoto et al. (Breast Cancer Res. Treat. 42: 87-90, 1997), U.S. Patent No. 5,681,543 A to Schmitt-Willich, et al., and Canto et al. (Gastrointestinal Endoscopy 44: 1-7, 1996) either alone or in combination, do not teach or suggest all the claim limitations of claims 33 and 36-39.

A. Yoshimoto *et al.* (Breast Cancer Res. Treat. 42: 87-90, 1997)

In the Examiner's Answer, the Examiner has maintained the rejection of claims 33 and 36-39 under 35 U.S.C. § 103(a) and rejected Appellants' arguments that Yoshimoto *et al.* does not teach or suggest a method for identifying the location of a lesion within the breast or breast ductal network by arguing that Yoshimoto *et al.* "...discloses that following pathologic examination of the mastectomized tissue, it was confirmed that the location of the wide-spread comedo carcinoma of mainly ductal carcinoma in situ coincided with the location of the lesion shown by MR galactography (Figure 2, page 89), which, in essence, is 'proof-of-principle' that MR galactography may be used to **pinpoint** the **exact** location of such lesions in the breast of patients." (emphasis added) (June 24, 2005 Examiner's Answer, page 14, lines 10-15). The Appellants respectfully disagree.

Yoshimoto *et al.* does not teach or suggest a method to pinpoint the exact location of lesions within a breast duct or breast ductal network. The Examiner has misinterpreted the facts of Yoshimoto *et al.* A clear reading of Yoshimoto *et al.* reveals that the MR galactography is useful for determining the degree and spread of disease, not the exact location of lesions. The case report in Yoshimoto *et al.* states that "[m]ammography showed extensive microcalcifications without abnormal opacity (Figure 1) and galactography showed widespread ductal abnormalities showing extensive intraductal-spreading carcinoma (Figure1B)." (page 87, column 2). The case report then goes on to state that the results of the new MR galactography "showed all portions of the entire discharge duct system and the surrounding area was enhanced after intravenous infusion of Gd-DPTA (Figure 2A-B)." (page 88, column 2) (emphasis added). The spread of previously diagnosed ductal carcinoma (via galactography observation of widespread ductal abnormalities) within the ductal system was confirmed by MR galactography and subsequent pathological examination. Both galactography and MR galactography are non-specific for breast cancer cells because attenuated ducts or filling defects may be caused by numerous benign conditions such as fibroadenomas and cysts. (see Dinkel *et al.*, The British Journal of Radiology, Vol 73, Issue 871 706-714; attached as Appendix A). Thus, contra to the Examiner's assertion, Yoshimoto *et al.* does not teach or suggest a method to pinpoint the exact location of lesions in the duct or ductal network of a breast because Yoshimoto *et al.* teaches the

use of galactography which uses a non-specific imaging agent for the of identification of abnormalities in breast ducts which may or may not be cancerous.

The Examiner continues to assert, on Page 15 of the Examiner's Answer, that the Appellants have manipulatively taken the statements out of Yoshimoto *et al.* out of context. The Appellants once again point to the exact wording found in Yoshimoto *et al.* which demonstrates that MR galactography is "somewhat inferior" to mammographic galactography in terms of differential diagnosis (see page 90; second column). Since MR galactography is "inferior" to mammographic galactography in terms of differential diagnosis (i.e., distinguishing normal from cancerous cells), and Yoshimoto *et al.* clearly states that mammographic galactography is problematic in determining the exact location of disease within a breast (page 88, Figure 1. legend), then it is axiomatic that MR galactography, although an improvement in helping determine the extent or spread of abnormal cells within a breast duct, is worse than mammographic galactography in detecting the exact location of cancerous cells in a breast duct. Thus, the Appellants have not taken the statements of Yoshimoto *et al.* out of context, but have highlighted the statements to show that Yoshimoto *et al.* teaches away from the claimed invention.

The Examiner then states on page 15 of the Examiner's Answer that the Appellants' argument that Yoshimoto *et al.* simply does not teach or suggest a method of identifying the specific location of a lesion within a breast duct or breast ductal network is not persuasive because "...the claims are not directed to a method of identifying the exact location of breast cancer cells , notable the claims are not directed to a method of identifying the *specific* or *exact* location of breast cancer cells within the breast. Although the claim language does not use the word "exact" or specific" in the preamble, it is inherently true that the methodology of the present claims would only identify the exact location of breast cancer lesions in a breast duct. Appealed claim 33 recites a method of delivering a compound into at least one breast duct and allowing the delivered compound to specifically bind to at least one breast cancer cell within at least one duct or ductal network and then washing the breast duct or ductal network with a solution to remove the non-specifically bound compound. Thus, it is axiomatic that the method of the present invention would be able to identify the specific or exact location of a lesion within

a breast duct because the identifying compound recited in the claim is only capable of identifying cancerous cells unlike the method taught in Yoshimoto *et al.* which is non-specific.

Thus, Yoshimoto *et al.* does not teach or suggest the present invention because it does not disclose all of the limitations of the pending claims either alone or in combination with any or the other prior art references. Accordingly, the premise on which the rejection is based, i.e. that Yoshimoto *et al.* teaches or suggests a method of identifying the specific location of a lesion within a breast duct or breast ductal network, is not supported by the evidence of record.

B. United States Patent 5,681,543 to Schmitt-Willich, *et al.* (the '543 patent)

The Examiner has maintained the rejection of claims 33 and 36-39 under 35 U.S.C. § 103(a) and rejected Appellants' arguments that the '543 patent does not teach or suggest the use of complexing agents to identify the specific location of lesions within breast ducts.

The Examiner reiterates that the '543 patent teaches "...conjugates of monoclonal antibodies specific for tumor-associated antigens and the disclosed gadolinium-containing polymer complexes are suitable for use in tumor diagnosis...including tumors of the breast..." (Examiner's Answer page 17, lines 9-12). The Appellants disagree.

The '543 patent teaches polymer-bonded complexing agents and pharmaceutical agents containing them for magnetic resonance imaging. The '543 patent does not teach or suggest the use of such complexing agents to identify the specific location of lesions within breast ducts. Nowhere in the '543 patent is there a description of an antibody or antibody fragment that would specifically bind to cancerous breast cells. Nowhere in the '543 patent is there a description of tumor-associated antigens which are specific for breast cancer cells. As previously mentioned, throughout the entire '543 document, there is but a single mention of breast cancer and that is in relation to a generic list of tumors, including tumors of the gastrointestinal tract, breast, liver, bladder, gonads and of melanoma, as potential targets for monoclonal antibodies. To suggest that the '543 is enabling for conjugates of gadolinium-containing polymer complexes with monoclonal antibodies specific for tumor-associated antigens of the breast is fallacious.

Also, the Examiner revisits Yoshimoto *et al.* and makes the argument that "...Yoshimoto *et al.* teaches the injection of gadolinium-DPTA into the breast duct to identify the location of such lesions by magnetic resonance imaging for the purposes of excising the lesions and

surrounding tissue by conservative surgery..." (Examiner's Answer page 18 lines 6-9). This statement is incomplete and misleading. Yoshimoto *et al.* teaches MR galactography through the administration of gadolinium-DPTA into the breast duct and intravenously to enhance the area around the breast duct. The injection of a contrast agent into a breast duct is the procedure known as galactography or ductography. As mentioned previously, the use galactography does not allow a practitioner to precisely identify cancerous cells in a breast duct (see page 88, Figure 1 legend). The use of MR galactography does not overcome this fundamental problem. How would the injection of gadolinium-DPTA intravenously result in an increase in the detection of cancerous cells inside a breast duct? The answer is simple. MR galactography does not increase the ability to detect cancerous cells, it only provides a practitioner an enhanced outline of the breast ducts within a breast. The practitioner can then use this enhanced image to estimate the potential extent or spread of disease in a breast duct or ductal system by looking for abnormalities in the ducts. As mentioned previously, a vast majority of abnormalities observed via galactography are not cancerous, but are benign (see Dinkel *et al.*, The British Journal of Radiology, Vol 73, Issue 871 706-714; attached as Appendix A). Thus, Yoshimoto *et al.* cannot teach a method for the detection of the specific location of cancerous cells within a breast duct because the methodology used in Yoshimoto *et al.* cannot distinguish between cancerous and benign conditions within the breast duct.

Thus, USP 5,681,543 does not teach or suggest the present invention because it does not disclose all of the limitations of the pending claims either alone or in combination with any or the other prior art references. Accordingly, the premise on which the rejection is based, i.e. that USP 5,681,543 teaches the administration of an identifying agent specifically targeted to lesions in the breast duct or breast ductal network, is not supported by the evidence of record.

C. Canto *et al.* (Gastrointestinal Endoscopy 44: 1-7, 1996)

The Examiner has maintained the rejection of claims 33 and 36-39 under 35 U.S.C. § 103(a) and rejected Appellants' arguments that Canto *et al.* does not teach or suggest procedures for the in vivo washing to remove non-specific bound diagnostic agents to increase the specificity of a diagnostic test. Canto *et al.* teaches the use of methylene blue in an endoscopic procedure to stain specialized columnar epithelium in the esophagus of patients. The Examiner argues that

"...because Canto et al. teaches or suggests that washing to remove excess or non-specifically bound diagnostic agents is performed in vivo during endoscopic procedures, which, given the routine and conventional inclusion of such 'washing' steps in diagnostic procedures in general, would have been understood to suggest that such steps improve the specificity of the test by reducing background noise, or the generation of non-specific, undesired signals." (Examiner's Answer, page 20-21). The Appellants disagree with the Examiners characterization of the "washing" step in Canto *et al.*

The Appellants agree that the washing step described in Canto *et al.* removes excess stain. However, the Appellants disagree with the Examiner's assertion that such a removal of excess stain increases specificity of the asasy. The stain used in Canto *et al.* is methylene blue, a non-specific stain. It is completely incongruous to state that the remove of excess non-specific stain from an *in vivo* assay will increase the specificity of the stain. The Examiner apparently has mistakenly interchanged the concept of specificity with sensitivity. The removal of non-specific stain from a diagnostic assay (i.e., excess stain) will increase the sensitivity of the assay (decreases the number of false negatives) while the removal of a specific binding agent in a diagnostic assay (i.e., non-specifically bound agent) serves to increase the specificity of the assay (decreases the number of false positives). Although both diagnostic assays have a "washing" step, the washing steps serve a completely different function in each of the corresponding assays.

The washing step described in Canto *et al.* is not applicable to the washing step specified in the method of the present invention because there is nothing in Cato *et al.* that suggests that methylene blue would selectively stain breast cancer cells in a breast duct.

Thus Canto *et al.* does not teach or suggest the present invention because it does not disclose all of the limitations of the pending claims either alone or in combination with any or the other prior art references. Accordingly, the premise on which the rejection is based, i.e. that Canto *et al.* teaches or suggests that washing to remove non-specific bound diagnostic agents can be performed by procedures to improve the specificity of the test by reducing background noise, or the generation of non-specific, undesired signals, is not supported by the evidence of record.

D. There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

The Examiner has rejected the Appellants' argument that there is no clear, particular suggestion or motivation in the prior art to combine the teachings in the applied references in the proposed manner to arrive at the specific method of identifying the location of breast cancer cells within a breast duct by providing a compound comprising a targeting agent coupled to an identifying agent; delivering the compound into at least one breast duct and allowing the delivered compound to specifically bind to at least one breast cancer cell, washing the breast duct with a solution to remove non-specifically bound compound and detecting the presence of the identifying agent within said breast duct.

The Examiner has argued that Yoshimoto *et al.* teaches a methodology to pinpoint the exact location of lesions within a breast duct or breast ductal network, that the'543 patent teaches the use of monoclonal antibodies specific for tumor-associated antigens and gadolinium-containing polymer complexes suitable for use in breast cancer diagnosis, and that Canto *et al.* teaches a washing step to remove non-specifically bound reagents from a diagnostic assay. The Appellants respectfully disagrees.

There is simply no suggestion or motivation to combine Canto *et al* with the teachings of Yoshimoto *et al* and the '543 patent. The Appellants has already addressed the deficiencies of Yoshimoto *et al.*, the '543 patent, and Canto *et al.* above. The differences between the methodologies of Canto *et al.,* Yoshimoto *et al* and the '543 patent are too great to believe that an ordinary person skilled in the art would have thought to combine the disparate teachings. Both Yoshimoto *et al.* and Canto *et al.* teach the use of non-specific imaging agents or dyes to identify tissues or cells which may or may be diseased or cancerous. The Examiner attempts to overcome this obvious deficiency by citing the '543 patent, however, the '543 provides no examples of breast tumor-associated antigens or antibodies which are specific to those antigens.

Applicants respectfully submit that the general teachings of administering non-specific contrast agents and dyes to patients are not sufficient to make Appellants' invention obvious and certainly *prima facie* obviousness has not been established under such conditions.

II. Whether claims 34 and 35 are patentable under 35 U.S.C. § 103(a) as being unpatentable over Yoshimoto et al. (Breast Cancer Res. Treat. 42: 87-90, 1997) in view of U.S. Patent No. 5,681,543 A to Schmitt-Willich, et al., U.S. Patent No. 4,628,027 A to Gay, Canto et al. (Gastrointestinal Endoscopy 44: 1-7, 1996), and U.S. Patent No. 6,168,779 to Barsky, et al.

A. United States Patent 4,628,027 to Gay, *et al.* (the '027 patent)

The Examiner has not presented a response to the Appellants' arguments as to why the "027 patent should not be considered as a prior art reference against the present claims.

B. United States Patent 6,168,779 to Barsky, *et al.* (the '779 patent)

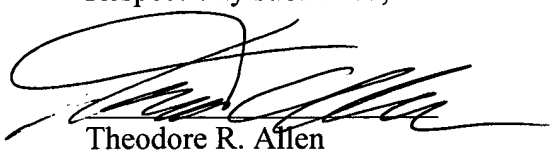
In the Examiner's Answer, the Examiner has maintained the rejection of claims 34 and 35 under 35 U.S.C. § 103(a) and rejected Appellants' arguments that the '779 patent simply does not teach or suggest a method of identifying the specific location of a cancer cells within a breast duct or breast ductal network. The Examiner restates that the '779 patent "...teaches the introduction of suitable diagnostic materials, such as contrast medium, into the breast ducts prior to imaging for the purpose of localizing cancerous lesions of the breast duct epithelium has been previously described by others..." (Examiner's Answer page 27, lines 3-6). The Examiner once again fails to point to any section of the '779 patent that teaches or suggests the use of a complexing agents to identify the location of cancerous breast cells within a breast duct or breast ducts. As mentioned in the Appellants' Brief, it is inappropriate to suggest that the '779 patent teaches a method of introducing contrast medium into breast ducts by pointing to other references.

Thus the '779 patent does not teach or suggest the present invention because it does not disclose all of the limitations of the pending claims either alone or in combination with any or the other prior art references. Accordingly, the premise on which the rejection is based, i.e. that '779 patent teaches or suggests the use of a complexing agents to identify the location of cancerous breast cells within a breast duct or breast ducts and the coupled compound is delivered to more than one duct on a breast, is not supported by the evidence of record.

CONCLUSION

In view of the arguments presented above, the Applicants contend that each of claims 33-39 is patentable. Therefore, reversal of the rejections under 35 U.S.C. §103(a) is respectfully solicited.

Respectfully submitted,



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Invention: **Methods for Identification, Diagnosis and Treatment of Breast Cancer**

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RESPONSE TO EXAMINER'S ANSWER IN AN APPEAL BRIEF

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